Congenital erythropoietic porphyria

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Congenital erythropoietic porphyria is a rare autosomal-recessive disorder of the porphyrin metabolism caused by the homozygous defect of uroporphyrinogen III cosynthase. High amounts of uroporphyrin I accumulate in all cells and tissues, reflected by an increased erythrocyte porphyrin concentration and excretion of high porphyrin amounts in urine and feces. Dermal deposits of uroporphyrin frequently induce a dramatic phototoxic oxygen-dependent skin damage with extensive ulcerations and mutilations. Splenomegaly and hemolytic anemia are typical internal symptoms. Skeletal changes such as osteolysis and calcifications are frequent. To date 130 cases of congenital erythropoietic porphyria have been published and are summarized here. Splenectomy, erythrocyte transfusions, and bone marrow transplantation have shown some beneficial effect. The best therapy is the avoidance of sunlight. In the two patients with congenital erythropoietic porphyria described here, oral administration of the oxygen quenchers ascorbic acid and α-tocopherol resulted in an improvement in the reduced hemoglobin and erythrocyte concentrations. (J Am Acad Dermatol 1997;36:594-610.)

The first description of congenital erythropoietic porphyria was published by Schultz[1] in 1874 and was termed *hydroa vacciniforme*. Congenital erythropoietic porphyria (CEP) was described in detail by Günther[2] in 1911 and termed *haematoporphyria* and *porphyria congenita*. The relation between the disturbance of the porphyrin metabolism and the resulting clinical alterations was underlined mainly by Fisher, Borst, and Koenigsdoerffer.[3-8] Waldenström,[9] in 1937, classified the porphyrias into CEP, acute intermittent porphyria (AIP), and porphyria cutanea tarda (PCT). A major advance was the differentiation between hepatic and erythropoietic porphyrias.[10] Recent classifications are based on the underlying genetic or acquired enzyme defect of porphyrin biosynthesis. Some summarizing reports on CEP have been published, especially in the 1960s, but recent updates are lacking.[11-24] CEP is an autosomal-recessive disorder of the porphyrin metabolism caused by the homozygous defect of the enzyme uroporphyrinogen III cosynthase; synonyms include uroporphyrinogen III synthase, uroporphyrinogen III isomerase, and hydroxymethylbilane hydrolase.[24, 26-37] Uroporphyrinogen III cosynthase converts hydroxymethylbilane—a linear tetrapyrrole—to the cyclic tetrapyrrole uroporphyrinogen III[24, 38] and therefore was formerly termed *isomerase*. Hydroxymethylbilane condenses spontaneously, 85% to the biologically inactive isomer I (= uroporphyrinogen I) and 15% to the physiologic isomer III (uroporphyrinogen III).

The accumulation of the biologically inactive type I porphyrins (particularly uroporphyrin I), mainly in bones, erythrocytes, skin, and teeth,[39-43] is accompanied by the excretion of large amounts of porphyrins in urine and feces.[21, 40, 44] Uroporphyrin and other porphyrin metabolites deposited in skin induce a phototoxic, oxygen-dependent damage (type II reaction) characterized by subepidermal blistering with severe inflammation.[45]

Approximately 200 case reports appeared in the literature (Table I), but many cases were published several times. This reduces the number of real CEP patients to approximately 130.*

CASE REPORTS

Case 1

A 49-year-old white woman has had pink-colored urine since birth. Severe phototoxic reactions with blisters, ulcers, and scars in light-exposed skin appeared after sun exposure. Vesicles occurred also after minimal trauma, particularly on the ears and nose. Extensive scars

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*References 1, 6, 7, 10, 11, 14-17, 19, 21, 22, 25, 30, 32, 34, 35, 39, 40, 42-44, 46-144.

and poorly healing ulcerations developed. Severe mutilation of all fingers developed. Oral prednisolone, 15 mg/day, induced an exacerbation of the skin lesions. Therapeutic trials with chloroquine, β-carotene, and H_1- and H_2-receptor blockers were without any benefit.

Examination revealed bullae of various sizes, ulcers, hyperpigmentation and hypopigmentation, severe fibrosis, and severe mutilations in light-exposed skin, particularly on the face, hands, and fingers (Figs. 1 and 2). Apart from the enlarged spleen, the results of a general physical examination were negative. X-ray studies of the hands showed massive mutilations with deformities and bone resorption of the terminal phalanges (Fig. 3).

Excessive concentrations of porphyrins, preferentially I-isomers, were detected in all samples. The highly carboxylated uroporphyrin predominated in urine and plasma, whereas in erythrocytes and feces, coproporphyrin was detected at highest concentrations, followed by uroporphyrin in erythrocytes and by protoporphyrin in feces. Isocoproporphyrin could not be demonstrated in urine or feces. The activity of the uroporphyrinogen decarboxylase was in the normal range. Severe hemolytic anemia was also present.

Case 2

A 32-year-old white man has had deeply red- to brown-colored urine since birth. In the third year of life severe light sensitivity was recognized. Light-exposed skin reacted with a severe phototoxic dermatitis, blisters, and ulcers with delayed healing; this was complicated by secondary infections and scarring with subsequent mutilation of the ears, nose, and hands.

Light-exposed skin showed hyperpigmentation, scars, and severe mutilations (Fig. 4). Lanuginous hypertrichosis was present on the arms and face. The patient had an extensive scarring alopecia on the head. Widespread ulcerations, scars, and skin fragility were noted. Closure of the eyes was impeded by bilateral lower lid ectropion, ptosis of the eyelid, and scleral atrophy. Microstomia, red-brown teeth with intense red fluorescence under Wood's light, and mutilations of hands and fingers with severe contractures were present. Splenomegaly was noted.

In urine, erythrocytes, plasma, and feces, excessive concentrations of porphyrins were demonstrated, preferentially type I-isomers. In the urine, higher carboxylated porphyrin metabolites, such as uroporphyrin and heptaporphyrin I, were the main porphyrins. In feces, coproporphyrin I and protoporphyrin were the main metabolites. In erythrocytes, protoporphyrin and uroporphyrin and in plasma uroporphyrin and coproporphyrin were the prevailing porphyrin metabolites. No isocoproporphyrin could be detected in urine or stool. Uroporphyrinogen decarboxylase activity was within the normal range. Severe hemolytic anemia (thrombocytopenia and leukocytopenia) was found.

DISCUSSION

The specific clinical picture enables diagnosis at a glance. Differential diagnosis includes severe forms of hepatoerythropoietic porphyria (HEP). In all published cases of CEP, patients show the typical history with extreme photosensitivity already evident in the first years. The diagnosis can be suspected because of the dark brown color of urine-soaked diapers with intensive red fluorescence under Wood's light[88, 145] and must be confirmed by analysis of porphyrins in urine and erythrocytes.

Genetic defect

CEP is an autosomal-recessive inherited disorder caused by a homozygous defect of the uroporphyrinogen III cosynthase with an activity of less than 10% in erythrocytes[30, 146] and fibroblasts.[147, 148] In cattle a comparable porphyria occurs with a reduction of erythrocyte uroporphyrinogen III cosynthase activity to approximately 5% of normal levels.[27, 28, 149-151] The variation in residual uroporphyrinogen III cosynthase activity among patients, particularly in cultured fibroblasts, indicates genetic heterogeneity.[27, 28] Uroporphyrinogen III cosynthase activity in presumed carriers of human CEP is about 50% of normal.[27, 146] No evidence of the existence of an inhibitor of the enzyme was found in erythrocytes of patients with CEP.[146] In parents and siblings of patients with CEP, a slightly increased uroporphyrin concentration has been demonstrated in erythrocytes.[14, 81, 116, 152, 153]

The analysis of a full-length complementary DNA (cDNA) encoding uroporphyrinogen III cosynthase was performed.[26, 32] The gene of the enzyme is localized on chromosome 10.[154] Genetic studies proved several mutations of the uroporphyrinogen cosynthase, including point mutations,[34, 36, 137, 155] deletion,[155] and insertion.[155] The most frequent C73R mutations with a replacement of cysteine by arginine are able to damage disulfide bonds and will influence the secondary structure of the enzyme.[36] Genotype-phenotype correlation should provide understanding of the remarkable clinical variability in patients with CEP. There is a strong correlation between the various mutations, the reduction of the uroporphyrinogen III cosynthase activity, and the severity or mortality of the disease:

Text continued on page 600

Table I. Summary of cases of congenital erythropoietic porphyria

Case No.	Year	Sex*	Nationality/ Race	Time of onset†	Hemolytic anemia‡	Splenomegaly§
1	1874	M	German	3 mo	N.D.	+
2	1898	M	English	4 yr	N.D.	N.D.
3	1898	M	English	3 yr	N.D.	N.D.
4	1903	F	German	1 yr	N.D.	–
5	1914	M	Italian	3 yr	+	+
6	1922	M	English	Birth	+	+
7	1924	F	English	5 yr	+	+
8	1926	M	Japanese	Birth	+	+
9	1926	F	English	Birth	+	+
10	1926	F	German	2 yr	+	+
11	1927	F	Japanese	Birth	+	+
12	1928	M	Japanese	16 yr	+	+
13	1928	F	Japanese	3 yr	+	+
14	1929	M	Italian	Birth	+	+
15	1929	M	German	Birth	+	+
16	1931	M	Italian	5 yr	+	+
17	1933	M	White	1 yr	+	+
18	1934	F	Argentinean	5 yr	+	+
19	1936	F	N.D.	4 yr	N.D.	N.D.
20	1938	F	Spanish	1 yr	N.D.	N.D.
21	1938	F	Spanish	2 yr	N.D.	N.D.
22	1938	F	Spanish	1 yr	N.D.	N.D.
23	1938	F	Spanish	2 yr	N.D.	N.D.
24	1938	M	Spanish	1 yr	N.D.	N.D.
25	1938	F	White	3 yr	N.D.	N.D.
26	1938	F	White	Birth	+	+
27	1947	F	White	Birth	–	+
28	1948	M	French	Birth	–	–
29	1948	F	French	Birth	–	–
30	1948	M	French	Birth	+	+
31	1948	M	Italian	3-4 yr	+	N.D.
32	1950	F	Bantu	11 mo	+	+
33	1951	F	Norwegian	2 mo	+	+
34	1951	F	White	1 yr	+	+
35	1953	F	Italian	Birth	+	+
36	1954	F	English	3 yr	+	+
37	1954	F	Polish	1 yr	+	+
38	1954	F	Polish	Birth	+	+
39	1956	M	Indian	6 mo	+	+
40	1956	M	Indian	1 yr	+	+
41	1957	M	Sudanese	9 mo	–	–
42	1957	F	Sudanese	7 mo	+	+
43	1957	M	Brazilian	4 mo	+	+
44	1957	M	Brazilian	10 mo	+	+
45	1957	M	Brazilian	10 mo	+	+
46	1958	F	Bantu	Birth	+	+
47	1958	M	German	Birth	+	+
48	1958	F	English	Months	+	+
49	1958	M	Indian	3 mo	+	+
50	1958	M	Indian	3 mo	+	+
51	1958	M	Egyptian	7 yr	+	+
52	1958	M	Egyptian	N.D.	N.D.	N.D.
53	1958	M	Egyptian	N.D.	N.D.	N.D.
54	1959	F	N.D.	2 yr	N.D.	N.D.

+, Symptom present; –, symptom not present; ∅, original paper not available; *C*, only coproporphyrin measured; *N.D.*, no data in cited paper [Ed: see footnotes to headings Hemolytic anemia and Splenomegaly]; *plasma*, only in plasma measured.

*M = 73 patients; F = 55.

†Time of onset; ≤ 1 yr, 75 patients; 2-5 yr, 28; 6-10 yr, 3; 11-20 yr, 6; > 20 yr, 11.

Total porphyrins			
Urine [nmol/24 hr]	Feces [nmol/gm dry wt]	RBC [nmol/100 ml]	Reference No.(s)
Red	N.D.	N.D.	1
Burgundy	N.D.	N.D.	46
Burgundy	N.D.	N.D.	46
Brown	N.D.	N.D.	47
Red	N.D.	N.D.	48
N.D.	N.D.	N.D.	11, 49
N.D.	N.D.	N.D.	11, 50
N.D.	N.D.	N.D.	51
50,400	105,600/24 hr	653	52, 53
Red	N.D.	N.D.	54
51,600	10,000	N.D.	55, 56
72,000	20,000	N.D.	56
Burgundy	N.D.	N.D.	56
Red	N.D.	N.D.	57
Red	N.D.	N.D.	7
Red	N.D.	N.D.	58
Red	N.D.	N.D.	59
∅	∅	∅	60
634‖	N.D.	N.D.	6, 61
Red	N.D.	N.D.	62
Red	N.D.	N.D.	62
Red	N.D.	N.D.	62
Red	N.D.	N.D.	62
Red	N.D.	N.D.	62
1842 (C)	4878/24 hr	N.D.	6
1044 4 (C)	10,212/24 hr	N.D.	6, 63, 64, 65, 66
N.D.	N.D.	N.D.	67
Red	N.D.	N.D.	68, 69
Red	N.D.	N.D.	68, 69
Red	N.D.	N.D.	68, 69
∅	∅	∅	70
22,248/L	2464	870	71, 72, 73, 74
13,057	1790	280	10, 76, 77
Red	N.D.	N.D.	78
Red	N.D.	N.D.	79
43,632	N.D.	614	10, 25
289,920	N.D.	N.D.	10, 81
343,584	7834	1531	10, 81
N.D.	N.D.	N.D.	19, 82
N.D.	N.D.	N.D.	19, 82
43,800/L	866	N.D.	72, 83, 84
33,384/L	791	N.D.	72, 83
Red	N.D.	N.D.	85
Red	N.D.	N.D.	85
Red	N.D.	N.D.	85
3360	1032	N.D.	72, 86
1116	245	585	87
155,040/L	4753/24 hr	322	88, 89, 90
Burgundy	N.D.	N.D.	19, 91
Burgundy	N.D.	N.D.	19, 91
Red	N.D.	N.D.	15
N.D.	N.D.	N.D.	15
N.D.	N.D.	N.D.	15
87,858	13,895	5827	37, 76

‡+, 81 patients; –, 19; N.D., 28.
§+, 77 patients; –, 19; N.D., 32.
‖Only type I isomers measured.

Table I. Cont'd

Case No.	Year	Sex*	Nationality/ Race	Time of onset†	Hemolytic anemia‡	Splenomegaly§
55	1960	M	Sardinian	6 yr	+	+
56	1960	F	Italian	1 mo	+	+
57	1960	M	Italian	1 mo	+	+
58	1960	M	French	3 yr	+	+
59	1961	F	Indian	Birth	+	+
60	1962	M	Bengalian	Months	–	–
61	1962	M	Bengalian	Birth	+	+
62	1963	F	Sicilian	Months	+	+
63	1963	F	Indian	3 mo	+	+
64	1963	M	German	Birth	–	+
65	1963	M	German	4 yr	–	+
66	1964	M	Irish	7 mo	+	+
67	1965	M	Indian	6 mo	–	–
68	1965	F	Indian	4 yr	–	+
69	1965	F	Indian	1 yr	–	+
70	1965	F	Bantu	53 yr	+	–
71	1967	F	English	7 mo	+	+
72	1969	F	American	Months	+	+
73	1970	F	N.D.	Months	+	+
74	1972	M	Canadian	1 day	+	+
75	1972	M	Canadian	Months	+	+
76	1972	M	German	2 yr	+	+
77	1973	M	Norwegian	4 yr	N.D.	N.D.
78	1973	M	French	1 day	+	+
79	1973	M	French	1 yr	N.D.	N.D.
80	1974	M	Hindu	14 yr	N.D.	N.D.
81	1975	F	French	1 yr	–	+
82	1975	M	Australian	58 yr	+	–
83	1975	M	Swiss	Days	+	+
84	1975	M	German	Months	+	+
85	1977	F	Irish	4 yr	+	N.D.
86	1977	M	Irish	1 yr	–	+
87	1977	M	Indian	Years	+	–
88	1977	F	French	8 mo	+	+
89	1978	F	Caucasian	3 yr	N.D.	+
90	1978	M	German	3 yr	N.D.	N.D.
91	1978	M	French	6 yr	N.D.	N.D.
92	1978	M	Greek	51 yr	+	+
93	1978	M	Libanesian	3 yr	+	+
94	1980	N.D.	American	4 mo	N.D.	N.D.
95	1980	N.D.	N.D.	N.D.	N.D.	N.D.
96	1980	N.D.	N.D.	N.D.	N.D.	N.D.
97	1981	M	French	55 yr	+	–
98	1981	M	Algerian	29 yr	–	–
99	1982	M	American	4 yr	+	+
100	1982	M	Caucasian	1 day	+	+
101	1983	F	Pakistani	5 yr	–	–
102	1983	M	French	15 yr	–	+
103	1985	M	Indian	25 yr	+	–
104	1985	M	White	55 yr	+	+
105	1986	M	N.D.	Months	N.D.	+
106	1988	F	Caucasian	Months	+	+
107	1988	M	Indian	2 yr	N.D.	+
108	1989	M	English	Months	+	N.D.

Total porphyrins			
Urine [nmol/24 hr]	Feces [nmol/gm dry wt]	RBC [nmol/100 ml]	Reference No.(s)
70,000	N.D.	N.D.	92
75,600	12,000/24 hr	1312	93, 94
19,200	3300/24 hr	241	93, 94
72,000	N.D.	N.D.	95
Pink	N.D.	N.D.	96
∅	∅	∅	97
∅	∅	∅	97
11,952	1653	697	98, 99
90,000	N.D.	N.D.	12
23,377	4486	2882	14
8686	N.D.	701	14, 100, 101
9840	N.D.	N.D.	40, 102
N.D.	N.D.	N.D.	103
N.D.	N.D.	N.D.	103
N.D.	N.D.	N.D.	103
15,060/L	1998	193	73
24,480	N.D.	N.D.	16, 17
100,320	1500	874	104
Red	N.D.	N.D.	89
+	N.D.	N.D.	105
+	N.D.	N.D.	105
70,800/L	N.D.	730	21, 106
N.D.	722	N.D.	39, 107, 108, 109, 110
1320	N.D.	N.D.	111
26,760/L	101	1320	21, 112, 113
13,014	1090	2100	42
4920/L	949	2552	22, 114, 115
12,444	2245	335	116
2778	N.D.	1418	117
28,512/L	N.D.	246	118
6556	13,529/24 hr	443	119
5079	25,644/24 hr	385	119
Red	N.D.	N.D.	120
13,896	1551	1028	121
N.D.	N.D.	N.D.	34
122,466/L	N.D.	1958	122
13,961/L	3680	1583	122
16,800	15,600	60	123
26,554	6137	54	124
N.D.	N.D.	N.D.	125
21,552/L	3009	1409	126
13,824/L	3260	1098	126
21,099/L	3230	760	30, 115
20,599/L	2489	614	30
25,440	421	226	44
188,000	N.D.	779	115, 127
15,320/L	1036	1249	128
3143/L	718	324	129
17,609	795	758	130
12,600	273	65 (plasma)	131, 132
N.D.	N.D.	N.D.	133
N.D.	N.D.	N.D.	32
9145	489 (C)	521	134
10,454/L	769	210	135

Table I. Cont'd

Case No.	Year	Sex*	Nationality/ Race	Time of onset†	Hemolytic anemia‡	Splenomegaly§
109	1989	M	Japanese	26 yr	–	–
110	1989	F	Japanese	36 yr	–	–
111	1990	F	Tunisian	Months	+	+
112	1990	M	East Europ.	51 yr	+	+
113	1990	F	Japanese	1 yr	+	+
114	1991	F	Pakistani	Months	N.D.	N.D.
115	1992	M	Algerian	17 yr	N.D.	N.D.
116	1992	F	Algerian	2 yr	N.D.	+
117	1992	F	Algerian	10 mo	N.D.	+
118	1992	F	Algerian	17 yr	N.D.	N.D.
119	1992	F	Algerian	13 yr	N.D.	N.D.
120	1992	M	Japanese	63 yr	+	–
121	1992	M	N.D.	Few yr	–	–
122	1993	M	Turkish	3 mo	+	–
123	1993	M	Turkish	Months	–	–
124	1993	M	Belgian	1 day	+	+
125	1993	M	Austrian	N.D.	N.D.	N.D.
126	1993	M	African	Months	+	+
127	1994	M	German	Months	+	+
128	1994	F	German	1 day	+	+

mild course, A66V/C73R; severe course, T228M/C73R; very severe course, C73R/C73R.[36]

Biochemical findings

Porphyrins. Urinary porphyrin concentrations are increased 100 to 1000 times with predominance of the higher carboxylated, water-soluble uroporphyrin I, which can be decarboxylated to heptacarboxylated, hexacarboxylated, and pentacarboxylated porphyrin, and coproporphyrin (as isomer I porphyrins). In addition, urinary excretion of uroporphyrin III and coproporphyrin III is also slightly increased.[12, 18, 20, 75, 156] The excretion of the porphyrin precursors, δ-aminolevulinic acid (δ-ALA) and porphobilinogen (PBG), is not increased in CEP.

Erythrocytes contain mostly large amounts of uroporphyrin I, but in some patients mainly zinc protoporphyrin has been demonstrated.[24, 109, 122] The enzyme deficiency causes the accumulation of uroporphyrinogen I in nearly all cells. Because uroporphyrinogen I can be decarboxylated by uroporphyrinogen decarboxylase, in erythrocytes and feces lower carboxylated porphyrins such as coproporphyrin I can be demonstrated.[157, 158] Erythrocyte protoporphyrin is normal or slightly increased. Fluorescence microscopic examinations of blood smears show a bright fluorescence of erythrocytes. This fluorescence is unstable and bleaches within 20 to 60 seconds.[159] Plasma concentrations of uroporphyrin and coproporphyrin probably derived from the increased porphyrin content of erythrocytes and of bone marrow erythroblasts are also elevated. The excessive hemolysis resulting in severe hemolytic anemia increases the plasma porphyrins and leads to massive porphyrin deposits in all tissues with the consequence of a severe photosensitivity.[10, 14, 37, 75]

Fecal porphyrin concentration is mainly dependent on porphyrin amounts excreted with bile, which contains preferentially the lipophilic coproporphyrin (predominantly type I isomer) and protoporphyrin. The accumulation of coproporphyrin results from decarboxylation of uroporphyrin preferentially by enzymes of intestinal bacteria.

In bone marrow the normoblast porphyrin content greatly exceeds that of circulating erythrocytes or other tissues and the typical red fluorescence originates predominantly from its nucleus or surface.[25, 160] Abnormal normoblasts have nuclear inclusion bodies containing hemoglobin and show red fluo-

Total porphyrins			
Urine [nmol/24 hr]	Feces [nmol/gm dry wt]	RBC [nmol/100 ml]	Reference No.(s)
14,363/L	3611	655	136
4122/L	990	215	136
N.D.	N.D.	N.D.	34, 137
12,672	82,800	N.D.	138
N.D.	N.D.	N.D.	43
89,589	N.D.	N.D.	139
2679	260	258	140
7460	249	3917	140
8135	N.D.	N.D.	140
938	407	3097	140
446	700	4234	140
12,348	58,608/24 hr	N.D.	141
100,999/L	6808/24 hr	642	35
396,600/L	N.D.	N.D.	142
316,800/L	N.D.	N.D.	142
86,549	4369	348	143
111,492/L	2450	1160	
4359/L	N.D.	636	144
208,068	2260	252	
56,584	1330	592	

rescence.[25] Normoblasts in the bone marrow of CEP patients contain primarily uroporphyrin (isomer I) and to a lesser extent coproporphyrin.[160] Excessive amounts of porphyrins are also found in the spleen and, less frequently, in the liver.[104] Porphyrins preferentially excreted in the urine are released from these normoblasts in the marrow, probably during the process of nuclear extrusion or by cellular destruction.[25, 157]

It is essential to confirm CEP by simultaneous determination of porphyrins in erythrocytes, urine, and feces with differentiation between isomers I and III.[161] In addition, absence of isocoproporphyrin in urine and stool and a normal value of uroporphyrinogen decarboxylase activity have to be demonstrated to refute HEP. The measurement of uroporphyrinogen III cosynthase activity is important mainly for scientific or genetic investigations. In all examined patients with CEP, the activity was reduced to less than 10%.[34, 146, 148]

In a pregnant woman without manifest porphyria, prenatal diagnosis of CEP could be achieved from amniotic fluid.[125, 162]

Hematologic findings. The excessive porphyrin concentrations in erythrocytes induce fragility with osmotic hemolysis.[37, 158] In fluorescence microscopy, preferentially precursors of erythrocytes can easily be identified as nucleated cells because of intensive red fluorescence (fluorocytes).[163, 164] A reduced red cell survival time and an ineffective erythropoiesis are pathogenic factors of the hemolytic anemia found in most patients with CEP.[165] Consequent spleen enlargement can be found in nearly all patients, and liver enlargement can be found in some.[165]

Hematoporphyrin added to red blood cells in vitro caused cell lysis on exposure to light.[166] Red cell lysates obtained from bovine and human subjects with CEP during the hemolytic phase formed mainly type I coproporphyrin after incubation with δ-ALA or PBG, whereas type III coproporphyrin was synthesized during the nonhemolytic phase.[74, 158, 167, 168] In human CEP the direct Coombs' test is occasionally positive[12, 169] and has been attributed to transfusion carried by reticulocytes.[16] Increased plasma iron turnover, decreased erythrocyte survival time, increased levels of unconjugated bilirubin, potassium, lactate dehydrogenase, and fecal urobilinogen are characteristic signs of the hemolytic process. In addition, transport proteins such as transferrin, ferritin,

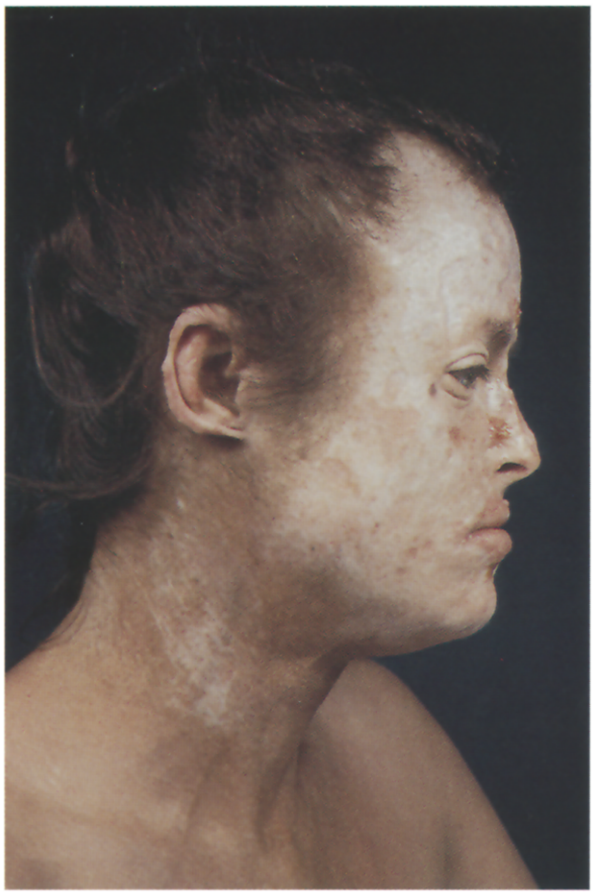

Fig. 1. Patient 1. Ulcers of various sizes, hyperpigmentation and depigmentation, severe fibrosis, and severe mutilations are present on the face, particularly on the nose and ears.

haptoglobin, and hemopexin are altered. The long-standing anemia can result in pancythemia accompanied by purpura and epistaxis.[73, 75, 88, 116, 123]

Clinical manifestations (Table II)

The severity of skin manifestations varies considerably among patients with CEP.[24, 38, 170] Skin photosensitivity most often begins in the first days of life and is induced especially by light with wavelengths around 405 nm (Soret band).[171] Increased amounts of porphyrins (uroporphyrin I) in the skin[87] and an intact cutaneous circulation with sufficient molecular oxygen supply are necessary to induce phototoxic reactions.[172, 173] Meyer-Betz[174] demonstrated in a self-experiment as early as 1913 that intravenous injection of hematoporphyrin produces severe cutaneous phototoxic reactions. Intradermal injections of porphyrins to normal probands also induced phototoxic reactions.[17] Biochemical studies confirmed elevated porphyrin concentrations in porphyric skin.[175] In CEP photosensitivity is usually severe and is manifested by second- or third-degree burns with formation of vesicles and bullae accompanied by ulcers or infections. The cutaneous symptoms in CEP have initially been termed *hydroa estivale* because of the increased severity during the summer months.[1] In the course of the disease, increased fragility, vulnerability, and ulcerations occur, followed by mutilations of fingers, hands, and face, particularly nose, cheeks, ears, lips, and forehead. Occasionally, sun-protected skin also shows an increased fragility and reduced wound healing (case 1). Nails and fingers may be deformed and partially lost. These cutaneous lesions are comparable, although to a minor degree, to those of PCT and HEP, pointing to uroporphyrin as a pathogenic photosensitizer and indicating that the degree of cutaneous damage is dependent on the porphyrin amount in tissues. Uroporphyrin plus UVA is able to induce increased formation of collagenase, which might be the basis of skin damage.[176] In addition, extensive hypertrichosis and pigment changes such as depigmentation and hyperpigmentation in minimally light-exposed areas are often found in CEP.

Ocular changes, such as blepharitis, cicatricial ectropion, conjunctivitis, and complete loss of the eyelashes and eyebrows, occur in CEP.[65, 119, 124] Scleral findings are interpalpebral fissures, and perilimbal sclera may exhibit pink fluorescence under Wood's light.[142, 177] Bilateral corneal scarring can occur, sometimes followed by blindness.[2, 16, 178] Scleromalacia with ultimate perforation of the lateral region of the corneal limbus,[179] decreased corneal sensitivity, pterygium,[11] optic atrophy, and retinal hemorrhage[65] have also been noted.

Porphyrin deposits cause reddish fluorescence of teeth in Wood's light examination and cause a reddish brown discoloration, even in normal light. Increased porphyrin deposits in dentine and enamel[180] may be due to an increased binding of porphyrins to dental calcium phosphate.[20] In seven cases of CEP an adult onset of signs and symptoms was noted.[73, 116, 123, 126, 138, 141] Erythrodontia is likely to be absent in late onset of disease because porphyrin deposition into dentine happens during tooth development.[73]

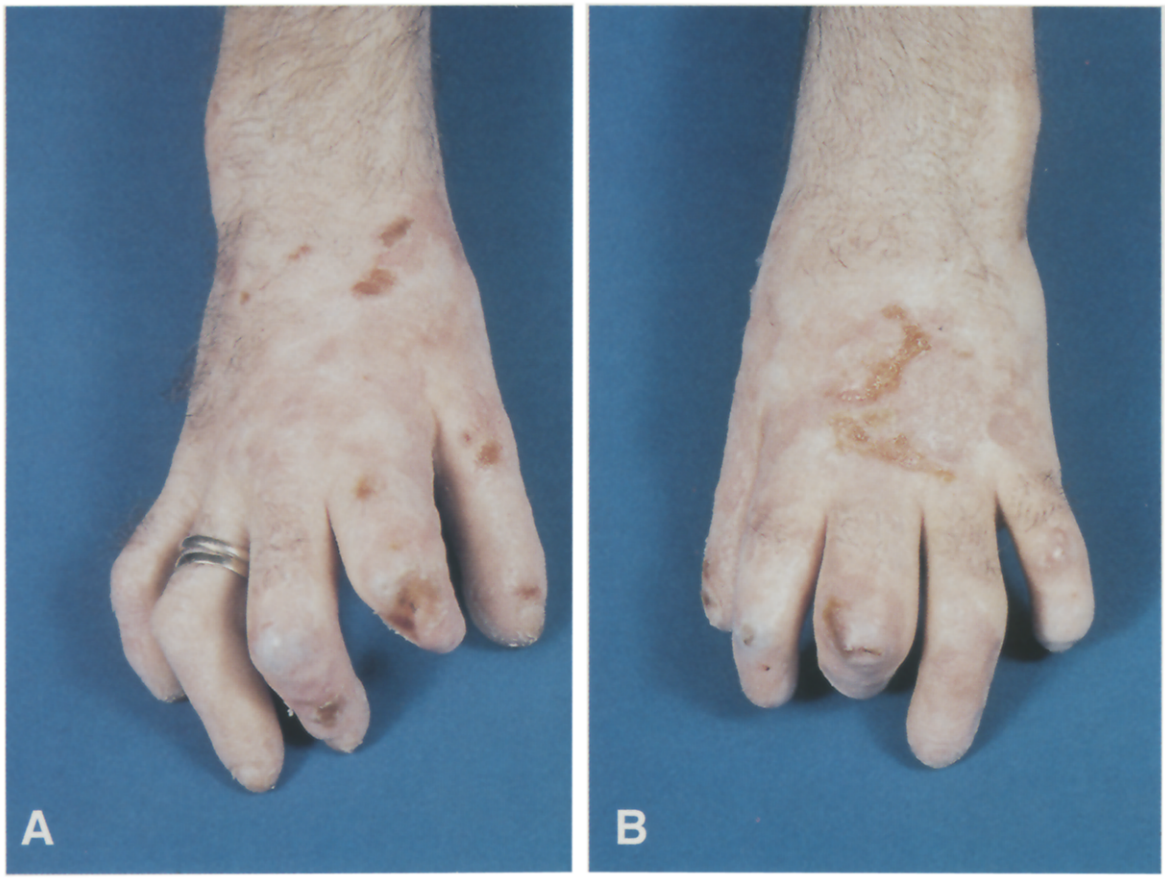

Fig. 2. Patient 1. Hyperpigmentation and depigmentation, ulcers, and fibrosis on the backs of both hands. Severe mutilation of all fingers with acromicria.

Histopathologic findings

The main histopathologic changes of CEP are bullae with dermal infiltrate. The vesicles occur subepidermally as in PCT, with increased scarring and hyalinization in the connective tissue. The roof of the subepidermal blisters is formed by the total epidermis. Histochemical examinations of the skin or liver show deposition of PAS-positive material in a perivascular distribution.[181, 182]

Skeletal changes

Severe osteolysis with mutilations is usually demonstrable in adults.[11, 85, 89, 101, 119, 124] X-ray studies showed severe contractures of the fingers and atrophy of the terminal phalanges similar to those in systemic scleroderma[89] and decreased density of the cancellous extremities.[11] Fine linear calcifications in the soft tissue deposited parallel to the phalanges were described; these are presumably related to the scar tissue.[89] The pathogenesis of the hand acromicria is still unknown. The radiologic findings of our patients include resorption of the terminal phalanges with acroosteolysis, cortical bone rarefaction, calcifications, accentuated trabecular patterns, and atrophy of the soft tissue of the fingers (Fig. 3). These calcifications are similar to those found in inflammatory soft tissue diseases, such as systemic sclerosis or dermatomyositis. Hypertrophy of bone marrow with osteopenia and a pattern of coarse trabeculae occur as the consequence of severe hemolysis and reduced bone mineralization similar to β-thalassemia major and sickle cell anemia.[9, 183, 184] In one patient numerous sclerotic and osteolytic round lesions of various sizes were demonstrated in the skull, maxilla, mandible, and pelvic bones,[43] complicated by multiple bone fractures after microtrauma.[115] Histomorphometric examinations of the bones showed a reduction in trabecular bone volume.[184] Vitamin D insufficiency secondary to sun avoidance may contribute to the man-

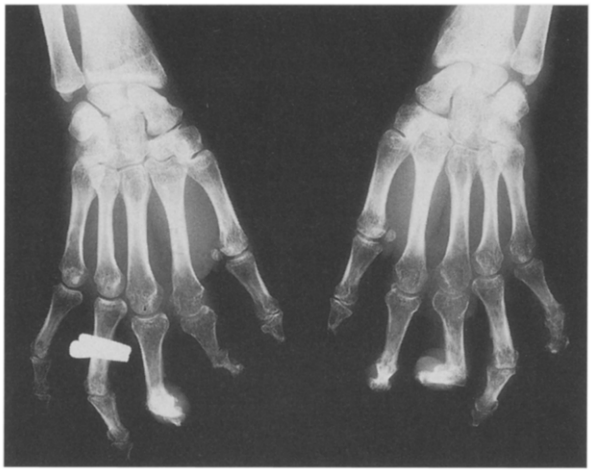

Fig. 3. Patient 1. Roentgenograms of both hands (anteroposterior). Severe loss of bone tissue with contractures and deformity. Resorption of the terminal phalanges resulting in severe mutilation.

ifestation of acroosteolysis[184] and can lead to secondary hyperparathyroidism and a mineralization defect.

In postmortem findings, all bones showed a brilliant orange-red fluorescence under UV light, which was also present in meninges, heart, lungs, liver, kidney, brain, and intestines.[42]

Therapy

To date no curative therapy is known. The only preventive measure is the absolute avoidance of exposure to sunlight. Topical sunscreen preparations are not well tolerated because of the severe skin damage most often found in exposed areas. Such complications as bacterial infections of the skin must be treated promptly with antibiotics to prevent scarring.

"Internal sunscreen" with oral β-carotene which is effective in some patients with erythropoietic porphyria[38, 185, 186] is almost ineffective in CEP,[24, 118] although some reports suggest that this oxygen quencher may improve light tolerance.[90, 110, 119, 127, 187-191] Sufficient serum levels of β-carotene, approximately 1000 μg/100 ml (upper normal limit 200 μg/100 ml/75 to 150 mg/day), are necessary to increase tolerance to sunlight.[192] Administration of *p*-aminobenzoate (12 gm per day),[21] chloroquine (125 mg twice per week),[16, 88, 90, 113, 122] and zinc sulfate (250 mg per day)[117] had no significant effects.

Another approach was the use of orally administered adsorbents such as charcoal and cholestyramine capable of binding porphyrins and of interrupting their reabsorption.[132, 193-195] Charcoal seems to be more effective than cholestyramine for reducing urinary, fecal, and plasma porphyrin levels[132, 195] with some loss of cutaneous photosensitivity.[194] However, high doses of drugs were needed.

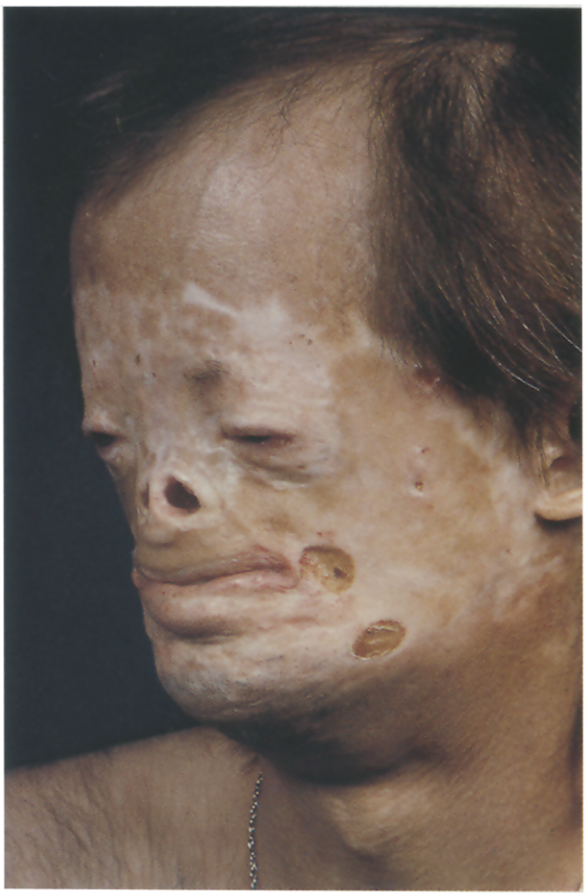

Fig. 4. Patient 2. On the face hyperpigmentation, particularly on forehead, and centrofacial hypopigmentation. Large ulcers with severe mutilations in the periocular area, nose, and mouth necessitate the use of a nasal epithesis.

Metabolic alkalization with sodium carbonate showed no substantial depletion of porphyrin stores, although there was an increase in urinary porphyrin excretion.[119]

An attempt to reduce erythropoiesis and corresponding endogenous porphyrin biosynthesis by means of erythrocyte transfusions with induction of polycythemia was successful.[133] During this treatment patients with CEP reveal a progressive increase in transfusion requirements, with the consequence of splenectomy because of excessive splenomegaly.

Table II. Clinical manifestations of congenital erythropoietic porphyria

Early clinical manifestations	Skin manifestations (sun-exposed skin)	Ocular manifestations	Internal manifestations	Osseous manifestations
Dark brown diaper	Burn, second- and third-degree	Seborrheic blepharitis	Splenomegaly	Atrophy and resorption of phalanges
Reddish brown urine	Edema	Cicatricial ectropion	Abdominal pain	Acroosteolysis
Crying babies	Blisters	Conjunctivitis	Hemolytic anemia	Reduced bone density
Erythrodontia	Superinfection	Loss of eyelashes and eyebrows	Headache	Cortical bone thinning
Photosensitivity	Scarring	Corneal scarring		Bone fractures
	Mutilations of the nose, lips, ears, and fingers	Scleromalacia		Linear calcifications in soft tissue
	Microstomia	Pterygium		Accentuated trabecular pattern
	Increased vulnerability and fragility of the skin	Optic atrophy		Hypertrophy of bone marrow with osteopenia
	Contractures of fingers	Retinal hemorrhage		Sclerotic and osteolytic round lesions
	Hyperpigmentation			
	Hypopigmentation			
	Hypertrichosis			

Consequent transfusion therapy reduced porphyrin excretion in about 50% of treated patients.[196] The complications of required regular transfusions, such as infections or iron overload, greatly reduce its usefulness.[13]

Intravenous hematin therapy is established in the treatment of the acute porphyrias, repressing δ-ALA-S and thereby inhibiting porphyrin biosynthesis.[197] The reduction of urinary porphyrin excretion is small and does not induce clinical remission in CEP. Porphyrin levels gradually increase over the ensuing months to pretreatment levels.[77, 138, 198] Plasmapheresis exhibited no change in porphyrin kinetics, which suggests that the plasma porphyrin pool has a high turnover rate and is not amenable to reduction by this form of therapy.[199]

In a patient with a myelodysplastic syndrome and adult-onset CEP, pyridoxal 5-phosphate was injected subcutaneously to treat the anemia. The urinary porphyrin concentration decreased to normal values, but the anemia gradually progressed.[141]

Numerous other therapeutic trials in patients with CEP were ineffective. Glucocorticosteroid therapy may improve anemia as well as thrombocytopenia in some patients[73, 116, 200] but not in others.[16, 73] Adenosine monophosphate was also without beneficial effect.[90]

In our two patients severe hemolytic anemia was the most pronounced life-threatening sign, apart from the extensive skin lesions. We assume that porphyrin-induced hemolysis is dependent on the formation of reactive oxygen radicals, and therefore we tried to quench the reactive species with α-tocopherol (0.5 gm per day) and ascorbic acid (1 gm per day). Under long-term therapy, hemoglobin and erythrocyte levels increased and no transfusions of erythrocytes were required.

Splenomegaly as a consequence of the severe hemolytic anemia is a nearly obligate sign in CEP (Table I), and in a few cases splenectomy improved hemolytic anemia by increasing of the life span of erythrocytes. The degree of hemolysis and the increased erythropoiesis were reduced in some cases[10, 78, 87, 88, 102, 138, 201] but not in others.[16, 104, 105] The beneficial effect of splenectomy on porphyrin excretion is most often of short duration.[104] A definite effect of the therapy could not be proven, and the improvement may have been partly due to transfusions given during surgery.[196]

Bone marrow transplantation should be the most effective treatment for a metabolic disorder with primary involvement of the bone marrow cells. One patient with CEP showed a complete clinical recov-

ery after bone marrow transplantation but died of cytomegalovirus infection.[202] The skin defects favor infections and complications, such as life-threatening sepsis.

Conceptually, gene therapy should prove the most promising development in inborn errors of porphyrin metabolism in the future.

Prognosis

Despite the limitations in treatment, the prognosis is not poor. Most patients with CEP survive into adulthood, and life expectancy is 40 to 60 years.

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